RESEARCHES ON SYNTHETIC CURARE ALKALOIDS

XIX. Synthesis of the Dimethyl Ether of Racemic Lyenzinine*

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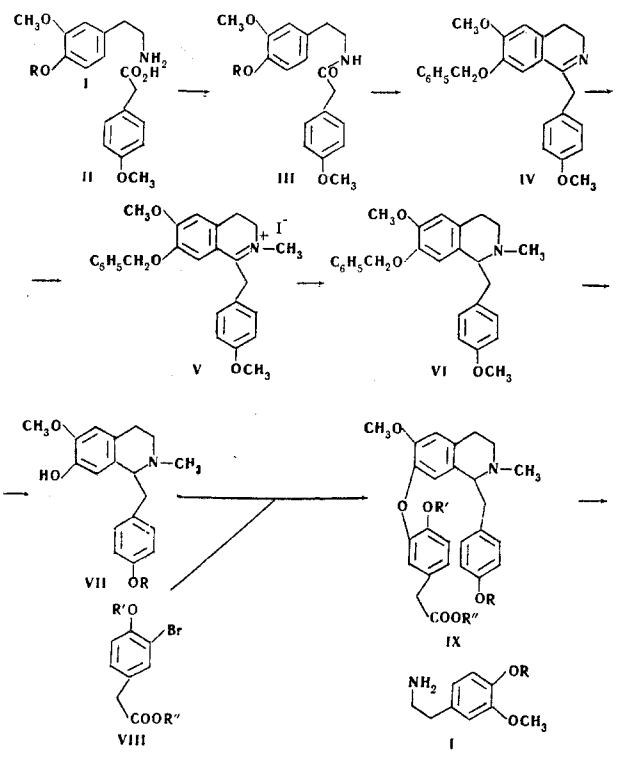
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 3, pp. 522–526, 1967

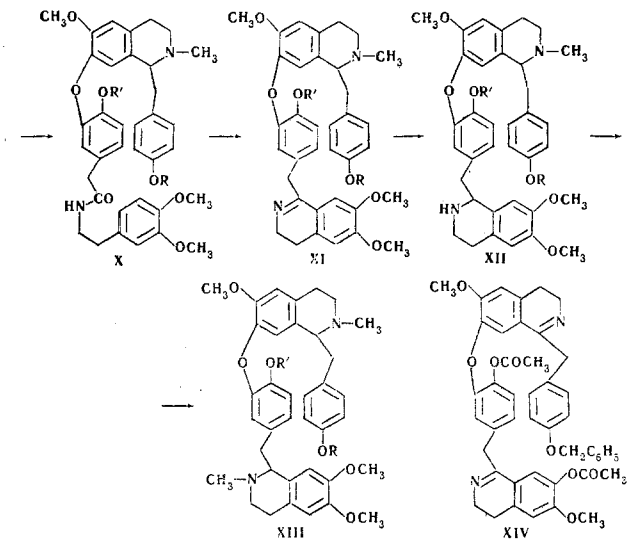
UDC 547.944.2 + 547.833 + 542.953

The dimethyl ether of racemic lyenzinine is synthesized by successive building-up of tetrahydroisoquinoline bases. The utility of this method for preparing hydroxy compounds is demonstrated. The benzyl analog of the diacetate of bisdehydroisolyenzinine is synthesized.

In order to prepare tubocurarine group alkaloids with different configurations at centers of asymmetry, and to identify compounds which we previously prepared, we developed a scheme of synthesis involving alternating formation of isoquinoline ring system [2]. The scheme is also of interest for preparing uncyclized analogs of chondodendrine, lyenzinine (XIII, R = R' = H, R" = CH_3) and isolyenzinine (XIII, R' = R" = = H, R = CH_3), which have been isolated from natural sources [3].

The dimethyl ether of racemic lyenzinine (XIII, R = R' = R" = CH_3) was synthesized by the following route:





β-(3-Methoxy-4-hydroxyphenyl)ethylamine (I, R = = H) was converted, by condensation with 4-methoxyphenylacetic acid (II) to the β-(3-methoxy-4-hydroxyphenyl)ethylamide of 4'-methoxyphenylacetic acid (III, R = H), which was then benzylated to the corresponding benzyl ether (III, R = $CH_2C_6H_5$). The same compound was obtained by condensing β-(3-methoxy-4-benzyloxyphenyl)ethylamine (I, R = $CH_2C_6H_5$) with methyl-4-methoxyphenylacetate. Cyclization was effected with zinc chloride under the usual conditions. The resultant 1-(4'-methoxybenzyl)-6-methoxy-7-benzyloxy-3, 4-dihydroisoquinoline (IV) was converted, via the methiodide V and the tetrahydro derivative VI, to 1-(4'-methoxybenzyl)6-methoxy-7-hydroxy-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (**VII**, R = CH_3). The double bond was reduced with zinc dust and acetic acid, or catalytically, using platinum oxide catalyst. The benzyl group was split off by hydrogenolysis in the presence of palladium.

The 4'-methyl ether of N-methyltubocurarine (**VII**, R = CH_3) was further condensed with the methyl ester of 3-bromo-4-methoxyphenylacetic acid (**VIII**, R' = R" = CH_3), and thus converted to 1-(4'-methoxybenzyl)-6-methoxy-7-(2"-methoxy-5"-carbomethoxymethylphenoxy)-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (**IX**, R = $CH_2C_6H_5$, R' = H, R" = C_2H_5) was prepared similarly by condensing the 4'-benzyl ether of N-methyltubocurarine (VII, R = $CH_2C_6H_5$) with ethyl 3-bromo-4-hydroxyphenylacetate (VIII, R' = H, R" = C_2H_5).

*For Part XVIII see [1].

Compounds IX ($R = R' = R'' = CH_3$) was further condensed with homoveratrylamine (I, $R = CH_3$), and the resultant amide, of structure **X** ($R = R' = CH_3$), was submitted to cyclization by the Bischler-Napieralski reaction to give the dihydroisoquinoline derivative **XI** ($R = R' = CH_3$). The double bond in the latter was reduced catalytically in the presence of platinum oxide, to 1-(4'-methoxybenzyl)-6-methoxy-7-[2''-methoxy-5''-(6''', 7'''-dimethoxy-1''', 2''', 3''', 4'''-tetrahydroisoquinolyl-1'''-methyl)phenoxy]-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (**XII**, $R = R' = CH_3$), and the mobile hydrogen of the latter methylated with formaldehyde and formic acid. The dimethyl ether of racemic lyenzinine **XIII** ($R = R' = R'' = CH_3$) was characterized as its hydrochloride. Cyclization of the β-{3-methoxy-4-[2''-acetoxy-5''-(β''-(3'''-methoxy-4'''-acetoxyphenyl)ethylcarbamidomethylphenoxy]phenyl}ethylamide of 4'-benzyloxyphenylacetic acid gave 1-(4'-benzyloxybenzyl)-6-methoxy-7-[2''-acetoxy 5''-(6'''-methoxy-7'''-acetoxy-3''', 4'''-dihydroisoquinolyl-1''''-methyl)phenoxy]-3, 4-dihydroisoquinoline (XIV), an intermediate in the synthesis of 4'-dimethylated derivative of lyenzinine (**XIII**, $R = R' = R'' = H$).

EXPERIMENTAL

β-(3-Methoxy-4-hydroxyphenyl)ethylamide of 4-methoxyphenylacetic acid (III, R = H). A mixture of 10.0 g β-(3-methoxy-4-hydroxyphenyl)ethylamine and 9.98 g 4-methoxyphenylacetic acid was heated for 1 hr at 190°–195° C in a current of N. After cooling, the reaction products were ground with ether. Yield 15.9 g (89.2%), mp 138.5°–139° C (ex EtOH). Found: C 68.86; H 6.87; N 4.72%. Calculated for $C_{18}H_{21}NO_4$: C 68.57; H 6.66; N 4.44%.

β-(3-Methoxy-4-benzyloxyphenyl)ethylamide of 4'-methoxyphenylacetic acid (III, $R = CH_2C_6H_5$).

a) A mixture of 4.6 g β-(3-methoxy-4-benzyloxyphenyl) ethylamine, 3.2 g methyl 4-methoxyphenylacetate, and 1.2 ml pyridine were heated together at 185°–190° C for 5 hr. Then the pyridine was vacuum-distilled off, the residue dissolved in $CHCl_3$, washed with dilute HCl, then with water, and dried over Na_2SO_4. After evaporating off the solvent, the residue was washed with ether, yield 6.13 g (84.5%), mp 114°–115° C (ex EtOH). Found: N 3.38; 3.41%. Calculated for $C_{25}H_{27}NO_4$: N 3.45%.

b) NaOEt (ex 0.962 g Na and 34 ml EtOH) was added to a solution of 13.5 g β-(3-methoxy-4-hydroxyphenyl)ethylamide of 4'-methoxyphenylacetic acid in 100 ml EtOH, then this was followed by 5.24 g benzyl chloride added over a period of 15 min. The reaction mixture was refluxed for 5 hr, filtered hot, and the amide which separated on cooling filtered off. Yield 13.01 g (75.5%), mp 114°–115° C (ex EtOH). Mixed mp with a specimen of the previous preparation, 114°–115° C.

1-(4'-Methoxybenzyl)-6-methoxy-7-benzyloxy-3, 4-dihydroquinoline (IV). A mixture of 10.15 g β-(3-methoxy-4-benzyloxyphenyl)ethylamide of 4'-methoxyphenylacetic acid, 100 ml toluene, and 13.86 ml $POCl_3$ was heated for 1 hr 30 min, by refluxing in a current of N. The toluene and excess $POCl_3$ was vacuum-distilled off, 30 ml EtOH added to the residue, and the whole heated to effect complete solution. On cooling the crystalline hydrochloride separated, yield 9.53 g (98.2%), mp 200°–201° C (decomp). Found: C 70.51; 70.77; H 6.18; 6.19; N 3.12; 3.38%. Calculated for $C_{25}H_{25}NO_3 \cdot HCl$: C 70.83; H 6.13; N 3.30%. Picrate mp 195°–196° (ex AcOH). Found: N 8.97; 9.25%. Calculated for $C_{31}H_{28}N_4O_{10}$: C 60.38; H 4.54; N 9.09%.

1-(4'-Methoxybenzyl)-6-methoxy-7-benzyloxy-3, 4-dihydroisoquinoline methiodide (V). A suspension of 14.75 g 1-(4'-methoxybenzyl)-6-methoxy-7-benzyloxy-3, 4-dihydroisoquinoline hydrochloride in 115 ml dry EtOH was neutralized by adding, with stirring, NaOEt (ex 0.795 g Na and 29 ml EtOH). After stirring for 15 min, 11.5 g MeI was added, and the whole then refluxed for 4 hr, and filtered hot. On cooling the filtrate deposited pale-yellow methiodide, which was filtered off and dried, yield 15.2 g (89.3%), mp 167–167.5° C (ex EtOH). Found: C 59.25: 59.08; H 5.33; 5.29; N 2.71; 2.58%. Calculated for $C_{26}H_{28}INO_3$: C 58.98; H 5.29; N 2.64%.

1-(4'-Methoxybenzyl)-6-methoxy-7-benzyloxy-N-1, 2, 3, 4-tetrahydroisoquinoline (VI). a) A mixture of 9.0 g 1-(4'-methoxybenzyl)-6-methoxy-7-benzyloxy-3, 4-dihydroisoquinoline, 250 ml MeOH, and 5.25 g AgCl was shaken for 1 hr. The AgI was filtered off, and the solvent vacuum-distilled off from the filtrate. The residue was pale yellow methochloride, yield 6.74 g (91.9%), mp 49°– 50° C.

A solution of 6.0 g methochloride in 250 ml AcOH plus 69 ml water was heated under reflux with 46.5 g Zn dust for 2 hr 30 min, the products filtered, cooled, and the liquid neutralized with ammonia. The base which separated was extracted with $CHCl_3$ (4 × 100 ml), and the solvent evaporated off. Yield of hydrochloride 5.39 g (90.4%), mp 47°–48° C.

b) A solution of 1.0 g methochloride in 20 ml EtOH was reduced by shaking in a hydrogenation apparatus, in the presence of 0.5 g PtO (30 min). The catalyst was filtered off, and the solvent vacuum-distilled off. Yield of hydrochloride 0.91 g (89.9%), mp 48.0°–49.5° C.

1-(4'-Methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (VII, $R = CH_3$). A solution of 0.88 g 1-(4'-methoxybenzyl)-6-methoxy-7-benzyloxy-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline hydrochloride in 30 ml MeOH was reduced catalytically, in the presence of 0.3 g Pd black (5 hr). The catalyst was filtered off, the solvent vacuum-distilled off, the residue dissolved in 10% NaOH, and unreacted starting material extracted with ether. Then the aqueous layer was made acid with HCl, and excess acid neutralized with ammonia. The precipitate of base was extracted with ether, dried over K_2CO_3, and the solution concentrated under

vacuum. Addition of an ether solution of HCl gas led to separation of the hydrochloride, which was washed with ether, and dried. Yield 0.47 g (68.4%), mp 160°–169° C (decomp). Found: C 60.47; 60.00; H 6.28; 6.49; N 3.67; 3.92%. Calculated for $C_{19}H_{23}NO_3 \cdot HCl \cdot H_2O$: C 60.20; H 6.53; N 3.80%.

1-(4'-Methoxybenzyl)-6-methoxy-7-(2"-methoxy-5"-carbomethylphenoxy)-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (IX, R = R' = R" = CH_3). A mixture of 1.65 g 1-(4'-methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline hydrochloride, 2.8 g methyl 3-bromo-4-methoxyphenylacetate, 1 ml dry pyridine, and 0.1 g precipitated Cu catalyst, was heated first for 10 min at 160°, then for 20 min at 170° C, and finally for 1 hr 30 min at 185° C. After cooling the reaction products were treated with 25 ml water and 300 ml $CHCl_3$. The organic layer was separated from the Cu, washed with 100 ml 5% NaOH, then with 200 ml water, and the solvent distilled off. The residue was ground with 5 ml dry ether, yield 1.24 g (53.4%), mp 123°–130° C. Found: C 69.9; H 6.81; N 2.85%. Calculated for $C_{29}H_{33}NO_6$: C 70.1; H 6.72; N 2.85%. Hydrochloride, hygroscopic compound, mp 138°–142° C. Found: C 65.68; H 6.67; N 2.26; 2.47%. Calculated for $C_{29}H_{33}NO_6 \cdot HCl$: C 65.97; H 6.45; N 2.65%.

1-(4'-Benzyloxybenzyl)-6-methoxy-7-(2"-hydroxy-5"-ethoxycarbonylmethylphenoxy)-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (IX, R = $CH_2C_6H_5$, R' = H, R" = C_2H_5). 1.2 g 1-(4'-benzyloxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline was dissolved in KOMe (ex 0.012 g K and 11 ml MeOH), the solvent distilled off, the residue dried at 100° C, powdered, 1.06 g precipitated Cu catalyst added, along with 1.2 g ethyl 3-bromo-4-hydroxyphenylacetate. The mixture was heated and stirred under N for 1 hr at 185°–190° C, cooled, the products dissolved in 100 ml benzene, the catalyst filtered off, and the filtrate concentrated to 10 ml, then chromatographed on a column of grade IV activity alumina. The oily material isolated from a benzene fraction, was treated with ethereal HCl, and converted to the hydrochloride, which was an amorphous substance, yield 0.63 g (33.9%), mp 80°–97° C (decomp). Found: C 74.01; H 6.60; N 2.65%. Calculated for $C_{35}H_{37}NO_6 \cdot HCl$: C 74.05; H 6.57; N 2.47%.

The methyl ether was prepared similarly, yield 41.2%. Hydrochloride mp 220°–224° C. Found: N 2.23%. Calculated for $C_{34}H_{35}NO_6 \cdot HCl$: N 2.37%.

1-(4'-Methoxybenzyl)-6-methoxy-7-{2"-methoxy-5"-[β"'-(3"', 4"'-dimethoxyphenyl)ethylcarbamidomethyl] phenoxy}-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (X, R = R' = CH_3). A mixture of 0.52 g 1-(4'-methoxybenzyl)-6-methoxy-7-(2"-methoxy-5"-methoxycarbonylmethylphenoxy)-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline, 0.4 g homoveratrylamine, and 0.5 ml dry pyridine was heated for 4 hr at 182°–185° C, in N. The pyridine was vacuum-distilled off, and the residue ground with dry ether, then dried. Amorphous substance, yield 0.57 g (85.1%). Hydrochloride, mp 101°–103° C (softened at 95°). Found: N 4.25%. Calculated for $C_{38}H_{44}N_2O_7 \cdot HCl$: N 4.21%.

1-(4'-Methoxybenzyl)-6-methoxy-7-[2"-methoxy-5"-(6"', 7"'-dimethoxy-3"', 4"'-dihydroisoquinolyl-1"'-methyl)phenoxy]N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (XI, R = R' = CH_3). Prepared from 1-(4' methoxybenzyl)-6-methoxy-7-{2"-methoxy-5"-[β"'-(3"', 4"'-dimethoxyphenyl)ethylcarbamidomethyl] phenoxy}-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (X, R = R' = CH_3), similarly to compound IV. Yield 64.4%. Hydrochloride mp 163°–168° C. Found: C 65.22; H 6.58; N 4.06; 3.96%. Calculated for $C_{38}H_{42}N_2O_6 \cdot 2HCl$: C 65.60; H 6.33; N 4.02%.

1-(4'-Methoxybenzyl)-6-methoxy-7-(2"-methoxy-5"-(6"', 7"'-dimethoxy-1"', -2"', 3"', 4"'-tetrahydroisoquinolyl-1"'-methyl)phenoxy]-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (XII, R = R' = CH_3). Prepared by catalytic reduction of the dihydroisoquinoline derivative XI (R = R' = CH_3) in the presence of PtO (3 hr), similarly to compound VI, yield 72%, mp 98°–100° C. Found: N 4.37%. Calculated for $C_{38}H_{44}N_2O_6$: N 4.47%.

1-(4'-Methoxybenzyl)-6-methoxy-7-[2"-methoxy-5"-(6"', 7"'-dimethoxy-N-methyl-1"', 2"', 3"', 4"'-tetrahydroisoquinolyl-1"'-methyl)phenoxy]-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline, dimethyl ether of racemic lyenzinine (XIII, R = R' = R" = CH_3). A mixture of 0.54 g 1-(4'methoxybenzyl)-6-methoxy-7-[2"-methoxy-5"-(6"', 7"'-dimethoxy-1"', 2"', 3"', 4"'-tetrahydroisoquinolyl-1"'-methyl)-phenoxy] N-methyl-1, 2, 3, 4-tetrahydroisoquinoline, 5 ml 85% formic acid, and 7.4 ml 34% formaldehyde, was heated for 5 hr at 95°–97° C. The products were treated with 50 ml 5% NaOH, and 300 ml ether. The organic layer was washed with water, dried over K_2CO_3, and concentrated under vacuum. The hydrochloride was precipitated by treating with an ether solution of HCl gas, yield 0.46 g (75.6%), mp 97°–99° C. Found: C 63.61; 63.60; H 6.93; 6.83; N 3.84; 3.81%. Calculated for $C_{39}H_{48}Cl_2N_2O_6 \cdot 1.5H_2O$: C 63.69; H 6.93; N 3.79%. Vacuum-drying (62° [7 mm], 3 hr) caused loss of half a molecule of water of crystallization. Found: C 64.21; 64.15; H 6.79; 6.85%. Calculated for $C_{39}H_{48}Cl_2N_2O_6 \cdot H_2O$: C 64.19; H 6.85%.

1-(4'-Benzyloxybenzyl)-6-methoxy-7-[2"-acetoxy-5"-(6"'-methoxy-7"'-acetoxy-3"', 4"'-dihydroisoquinolyl-1"'-methyl)phenoxy]-3, 4-dihydroisoquinoline (XIV). Prepared by cyclizing the β-{3-methoxy-4-[2"-acetoxy-5"-(β"'-(3"'-methoxy-4"'-acetoxyphenyl) ethylcarbamidomethyl)phenoxy} ethylamide of 4'-benzyloxyphenylacetic acid, similarly to compound IV. Hydrochloride, colorless crystalline compound, mp 160°–161.5° C. Found: C 65.11; H 5.52; N 3.32; 3.23%. Calculated for $C_{45}H_{42}N_2O_8 \cdot 2HCl \cdot H_2O$: C 65.14; H 5.55; N 3.38%. Base mp 88°–91° C. Found: C 71.78; 71.71; H 5.41; 5.36; N 3.67; 3.72%. Calculated for $C_{45}H_{42}N_2O_8 \cdot H_2O$: C 71.43; H 5.53; N 3.71%.

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28 July 1965

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